

**KETAMINE EFFICIENCY IN TREATMENT OF  
CHRONIC PAIN WITH AN ADDITIONAL  
INFLAMMATION: EXPLORATION OF THE  
KYNURENINE PATHWAY. A randomized, placebo-  
controlled, double-blind study.**

**Acronym: KEKU1 study**

**NCT number: Not available yet**

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**Cyril QUEMENEUR**

**V1\_2 : 12 / 30 / 2017**

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Insurance number: No. 124-626 SHAM  
EUDRA Registration: 2017-003930-10  
Clinical trial Registration: current  
REF. CPP: CPP PARIS X

**Promoter**

REDAR association  
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104 boulevard Raymond Poincaré, 92380 Garches

### Team

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Work under the responsibility of Pr. Valeria MARTINEZ.

### Partners:

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### Study site

Anesthesia Department.

Raymond Poincaré hospital.

104 boulevard Raymond Poincaré, 92380 Garches

### SUMMARY OF THE STUDY KE - KU1 STUDY

<b>Rational</b>	Is the kynurenine pathway involved in hyperalgesia. This pathway is activated by inflammation. Ketamine interacts with the kynurenine pathway and inflammation. Our working hypothesis are: ketamine clinical effects on neuropathic pain are more important in presence of systemic inflammation. The mechanism of action is through the kynurenine pathway.
<b>Type of study</b>	Interventional, randomized clinical, versus placebo
<b>Main objectives</b>	1) Show a better clinical efficiency of ketamine in chronic pain in patients with an inflammatory component. 2) Explore the anti-inflammatory activity of ketamine through Kynurenine pathway
<b>Start - end of the study</b>	January 2018-October 2018 as part of a Pharmacology M2.
<b>Duration of patient follow-up</b>	1 week.
<b>The study period</b>	6 months of inclusion.
<b>Population</b>	Adult spinal cord injured (BM), with chronic neuropathic pain (DN). 4 groups: BM with DN with bedsore (ulcer pressure) Ketamine group / group Placebo

	BM with DN without bedsore Ketamine group / group Placebo
<b>Intervention</b>	Infusion of ketamine 1 mg / kg in IVSE on two hours vs infusion 0.9% Nacl
<b>Primary endpoint</b>	Decrease the intensity of neuropathic pain evaluated at the moment on a numeric scale of 10 points to H4. Comparison by two groups.
<b>Criteria for secondary judgment</b>	Score of NPSI (Neuropathic pain symptom inventory) to H0, J1, J4, J7 NPSI underscore; H0, J1, J4 J7 Auto assessment of numeric pain scale every days from J0 to J7. Improvement rate of pain and mood during the week following the infusion. Score of depression HADS (Hospital Anxiety Depression Scale) J0, J7 Body area pain: H0, J1, J7. Ketamine side effects Plasma dosage of serotonin (5-HT) kynurenine (KYN), indoleamine 2, 3-dioxygenase 1 (IDO1) activity (ratio KYN/TRP), kynurenic acid (KA) and quinolinic acid (QA), as well as 3 proinflammatoire cytokyne it-1 $\beta$ , IL-6, and TNF - $\alpha$ before the infusion and infusion H4.
<b>Calculation of workforce</b>	The gap type of instant pain score is 1.4 on the same model. We considered that an improvement of 30% in the score of the intensity is significant clinical relief. Based on these figures and assuming a risk $\alpha = 0.05$ and a power of $1 - \beta = 0.90$ , and using a one-sided Student's T test for a comparison of the 2 to 2 groups the minimum calculated sample size is 12 patients analyzed by Group (i.e. a total of 48 patients).
<b>Conduct</b>	Inclusion of patients from the pain consultation and services of hospitalization of the spinal cord injured to hospital Raymond Poincaré Clinical evaluation and blood test prior to administration of ketamine Administration ketamine in SSPI, scopes. Blood test in 4 hours post end of administration Assessment baseline pain, H1, H4, J1, J4, J7. Assessment baseline depression, J0 and J7.
<b>Direct benefit</b>	Patients may benefit from treatment with Ketamine on their refractory neuropathic pain and monitored pain specialist

### **Rational:**

#### **1) The kynurenine pathway : a common way of hyperalgesia and depression.**

The kynurenine pathway is the way of tryptophan metabolism (figure 1). This path is involved both in depression and pain, two diseases often associated (1) .

The indoleamine 2, 3-dioxygenase (IDO) is an enzyme modulating the kynurenine metabolism. It has been shown that inflammatory cytokines may activate IDO, which would induce a decrease tryptophan by direction preferred to the path of the kynurenines, which can lead a deficit in serotonin and in consequence depression (2). One of the products of degradation of the kynurenine is quinolinic acid, a NMDA agonist receptors. NMDA receptors are involved in Central sensitization of the pain with as consequence an amplification of the painful message manifesting by an hyperalgesia.

#### **2) Kynurenine pathway activation by inflammation.**

A large number of experimental studies showed the important role of pro-inflammatory factors in the pathogenesis of chronic pain and depression (3-6) . The role of the pro-

inflammatory cytokines in the activation of the indoleamine 2, 3-dioxygenase (IDO) was widely reported and is a key action in the pathophysiology of the comorbidity of pain and depression (7-9) .

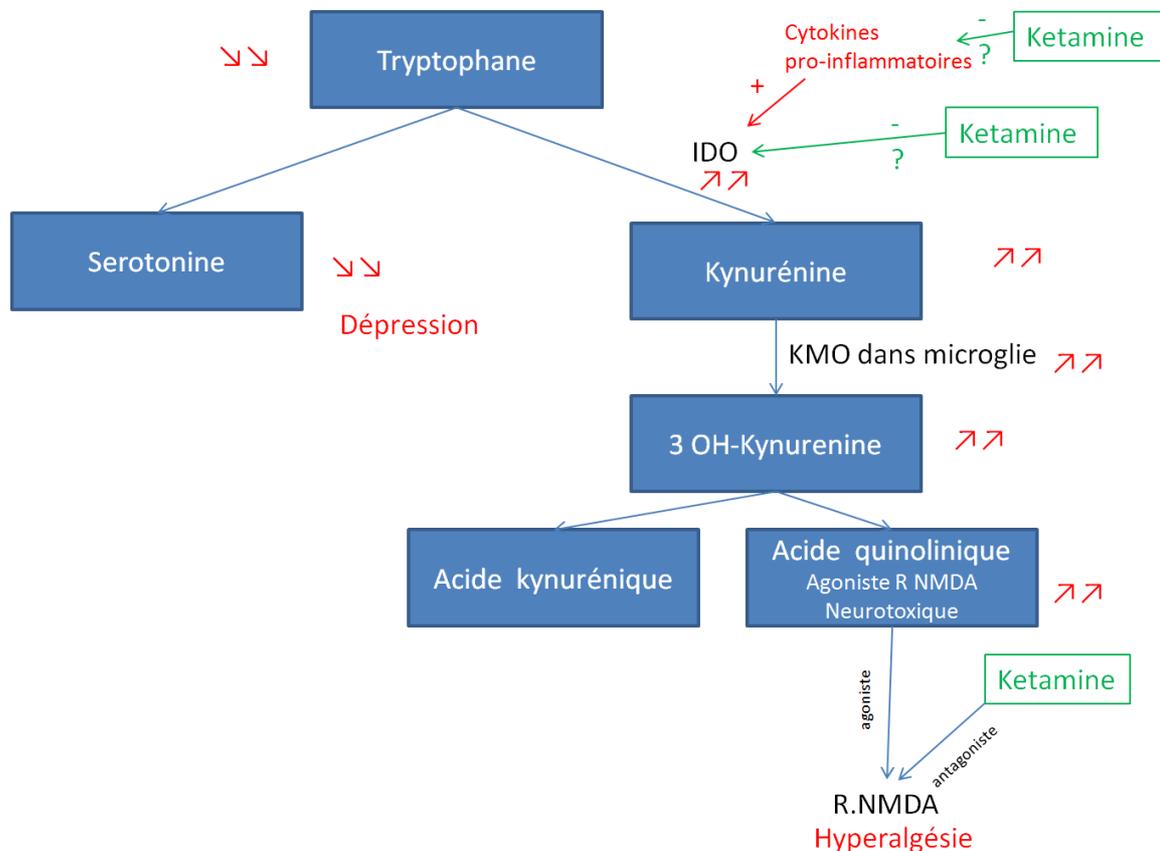
Several experimental and clinical work related the IDO enzyme is activated by systemic inflammation (10). This activation is found in several chronic inflammatory diseases (cancers, rheumatologic, inflammatory cardiovascular diseases). More recently its activation was highlighted in patients with the irritable bowel syndrome (11,12) . This path seems to activate quickly in the early hours after tissue trauma in models of various surgery (coronary bypass surgery, thoracic surgery, hysterectomy) (13,14) .

### **3) Interaction of ketamine on kynurenines.**

There are many mechanisms of action for ketamine. But more recently efficacy of ketamine in inflammatory so-called depressions and experimental studies addressing the inflammatory aspects common pain and inflammation have attracted our attention to the kynurenine pathway (15) (figure 1). Ketamine has shown a role towards the kynurenines in models of experimental pain (9,16,17). The ketamine has an antidepressant effect in fast action potentially by the inhibition of proinflammatory cytokines (18,19)(20). The rate of Interleukin 6 plasma would be predictive for efficiency of ketamine in a depressed patient population (21). Although there is a beam of clinical and paraclinical arguments about the role of IDO in the development of inflammation-induced depression, its role in pain is less explored in humans. However, experimental studies in animals showed the involvement of the path of kynurenines both in pain and depression. Kim and al (9) in a model of inflammatory pain in rats showed a relationship between the intensity of the thermal and mechanical allodynia and the concentration in mRNA of IDO, as well as of its enzymatic activity measured by the kynurenine/tryptophan ratio and that the rise of the concentration in IL6 in the brain.

Concomitantly, ketamine would reduce the concentration of intracerebral cytokine IL-6, IL-1 (6) , IDO, KYN/TRP ratio and increase the ratio of 5 HT / TRP.

Finally, Wang in 2011 shows in a model of neuropathic pain in animals, the benefit of a single dose of ketamine on depressive behaviors induced neuropathic pain in the rat (16) .



**Figure 1 ways of tryptophan metabolism** (in blue) adapted by Walker (15) . In the presence of inflammation (in red), assumption of action of ketamine (in green)

### Information about the product being designed: ketamine

#### Summary of clinical and experimental studies on the product.

Used in low doses, ketamine has a powerful anti-hyperalgesic effect. She is the only powerful antagonist of the N-methyl-D-aspartate (NMDA) receptor available today in clinic. The NMDA receptor is known to play an important role in the phenomena of Central sensitization. It is widely used in perioperative to diminish the pain and the consumption of opioids. His action in acute pain is all the more important that surgery is traumatic (22) . Preventive effects of the postoperative pain required are

mentioned (23). On the other hand, robust and sustained antidepressant effects after a single intravenous infusion of low-dose ketamine in patients are reported (24). Ketamine is also used off-label based on recommendations of good practices for dealing with the chronic pain (25).

However, systematic reviews recent questioning the interest ketamine in chronic pain rebel related a great heterogeneity in the results related to the great disparity in the populations studied and the administered dosages (26)(27)(28).

It appears that efficiency is obtained for high doses total (> 0, 5 mg/Kg) administered slowly over an hour on (29). These reviews also highlight the need to better identify patients.

#### Information on benefits and risks of the product.

The benefit expected from the product's effectiveness on refractory chronic neuropathic pain with a pain relief in these patients who are beyond all other types of pain treatments.

Ketamine at a dose of 1 mg / kg is well tolerated in clinic and in various studies around ketamine. The contraindications of ketamine are allergy, severe hypertension, severe heart failure: patients excluded from our study. In the conditions of the study, dosage and duration of infusion, the risk of adverse effect is minimal.

The most common side effects are: drowsiness, euphoria, hallucinations, tinnitus, nightmares and disorientation, nystagmus (rhythmic oscillation of the eyes), arterial hypertension and tachycardia. Patients being scoped and monitored medically in post interventionnal oversight room, the slightest side effect will be detected and treated.

In our study the administration will be intravenously, it will be a single infusion of ketamine at a dose of 1 mg/kg, over a period of two hours. As mentioned previously, it appears that the effectiveness of the product in clinical studies appears to doses higher than 0, 5 mg/kg administered slowly on over an hour (29). Where our choice of infusion is over 2 hours. We have chosen a single infusion to avoid the effects of the repeated infusion over several days which showed liver adverse effects in the recent literature with doses regimens of ketamine very important. (36)

The clinical trial will be conducted in accordance with the Protocol presented in this document following compliance with good clinical practices.

#### **Description of the study population: spinal cord injury patients with chronic pain with or without bed sore (ulcer pressure)**

The incidence of spinal cord injury (SCI) is about 20 / million residents in France, more than 1,200 new cases per year, and prevalence is more than 250 / million residents, or about 20,000 patients in France. For SCI patients, the prevalence of chronic pain is 65-85%, of which 40% are neuropathic and one-third are severe. Neuropathic pain are the hardest to relieve and there is a strong correlation between their presence and a difficult becoming both psychological, physical and social. Pain affects sleep, quality of life, interpersonal, socio-professional rehabilitation or return to work. His prognosis is not good with a low long term

resolution(30). There are few studies showing the effectiveness of ketamine administered by intra venous infusion in the treatment of refractory chronic pain medication (29). The recent literature reviews report the results in central neuropathic pain, especially in SCI patients (28,29).

50 to 80 percent of the SCI patients will develop at least an ulcer pressure over a lifetime. These pressure ulcers like all chronic wounds are factors of inflammation. This chronic inflammation in the zone under the injury, often insensitive, is a factor of awareness of the central nervous system. It is common to observe an exacerbation of chronic central neuropathic pain patients during inflammation. On the other hand, the clinical observations report often spectacular efficiency of ketamine on the neuropathic pain in those patients with bedsores.

Is this effect explained by a role on the kynurenine pathway in this population?

Would ketamine be more effective in this population?

### **Working hypothesis**

The hypothesis that we raise, is : ketamine has an anti hyperalgesic action by anti inflammatory effects by interacting with the kynurenine pathway.

We test this hypothesis in a clinical study with ketamine in chronic pain patients with or without associated inflammation. Our choice of population is patients with spinal cord injury with central neuropathic pain. Part of this patient population frequently suffers from pressure sores which leads to chronic inflammation.

### **Trial purpose and goal:**

Our clinical research aims to test the two following hypotheses

**(1) The ketamine clinical effects on chronic neuropathic pain are more important when there is an associated inflammation.**

**(2) Its action is through interaction on the kynurenine pathway.**

### **Methods**

#### **Population**

The selected population is a population of SCI patients with central neuropathic pain at the level of injury or under injury, chronic (more than three months).

Patients are recruited through specialized consultation pain or bedsores consultation or through consultation and hospitalization in service of physical medicine and rehabilitation in hospital Raymond Poincare in Garches. This hospital is specialised in SCI management. The

Protocol will be proposed in a consultation of usual follow-up or hospitalization. The treatment will be initiated remotely, in a subsequent consultation scheduled apart of their follow-up.

Four groups of patients will be included:

Group 1: SCI with central neuropathic pain **with bedsore receiving ketamine infusion.**

Group 2; SCI with central neuropathic pain **with bedsore receiving placebo.**

Group 3: SCI with central neuropathic pain **without bedsore receiving a ketamine infusion.**

Group 4: SCI with central neuropathic pain **without bedsore receiving a placebo infusion.**

**Description of treatment (dosages, forms, packaging) and preparation of the product.**

Ketamine: infusion IVSE of 1 mg/kg during 2 h in a 50 cc syringe Luer Lock BD Plastipack (100mg of Ketamine was 2 blisters 50mg / 5mL in a syringe of 50cc or a concentration of 2 mg/cc, speed = weight of the patient/4 mL/h).

A 50cc syringe Luer Lock Plastipack BD composed of Sodium chloride 0, 9% will be administered in the placebo group at the same rate in mL/h (weight of the patient/4 mL/h).

The 2 products are transparent, it will be impossible to differentiate the two products with the same packaging or a syringe with Luer Lock Plastipack BD 50 cc with a standard Extender for syringe Luer Lock.

Both products will be prepared by a nurse of SSPI, which won't participate in the study. The investigator responsible for the evaluation of the patient and the patient will remain blind to the administration of the product. Statistics will also be blind. Each syringe will be labeled only with patient number inclusion.

The infusion will be conducted in post operative monitoring room of the hospital Raymond Poincare in Garches, patients will be scoped and monitored for 1 h after the end of the infusion.

**Design of the study**

The study will be driving double blind, neither the patient nor the evaluator clinician will know product administered to the patient. The statistician who will analyze the data in the course of the study will be blind of the group in which the patient is located.

Randomization will be ensured by a randomization table created proactively using the R software between the two groups. The blind will be maintained through sealed envelopes. The post interventional monitoring room nurse will be the only one to know the contents of the envelope for the preparation of the drug. The investigator and the patient will remain blind to the treatment administered. The packaging is identical, the blind will be maintained throughout the study.

To ensure maximum safety, the traceability of the product will be provided with lot number of Ketamine or informed administered Placebo on a pre established for each patient, form that you will find in the appendix to the project.

Any potential adverse event will be supported by physicians anesthesiologists responsible resuscitators of post operative monitoring of the hospital Raymond Poincaré, then transmitted instantaneously in pharmacovigilance and to the ANSM.

### **Clinical and paraclinical evaluation during the test.**

*Before administration of ketamine, we will evaluate clinical way:*

The intensity of neuropathic pain evaluated at the moment on a numeric scale of 10 points at H0.

The score NPSI Neuropathic Pain Symptom Inventory comprising 12 questions, each question will be analysed: burning pain, pain to type of vise, compression pain, number of hours painful in the past 24 hours, such painful crises of electrical discharges, painful crises in type of knife, number of painful crises in the last 24 hours, presence of pain caused or increased pressure on the painful area, presence of pain caused or increased by the contact with a cold object on the painful area, presence of stinging, tingling presence.

HADS depression scale with 14 questions: Seven concerning anxiety and seven concerning depression.

The painful area evaluated on mapping by the subject before administration of ketamine then during follow-up.

### ***Paraclinical:***

A blood sample will be realized before the infusion of ketamine with dosage of: serotonin (5-HT), kynurenine (KYN), indoleamine 2, 3-dioxygenase 1 (IDO1) activity (ratio KYN/TRP), kynurenic acid (KA) and quinolinic acid (QA). as well as 3 proinflammatoires cytokines it-

1 $\beta$ , IL-6, and TNF -  $\alpha$ . then a new dosage to 4 hours from the end of the infusion in the hospital or outpatient service and will include the dosage of: serotonin (5-HT), kynurenine (KYN), indoleamine 2, 3-dioxygenase 1 (IDO1) activity (ratio KYN/TRP), kynurenic acid (KA) and quinolinic acid (QA), as well as 3 proinflammatoires cytokines it-1 $\beta$ , IL-6, and TNF -  $\alpha$ .

### **Duration of participation of the subjects:**

The protocol will take place in the post operative monitoring room for infusion with 2-hour infusion, care of one hour after the end of the infusion in post operative room and then four hours in the hospital.

Either a minimum of passage to the hospital in 7 hours.

For hospitalized patients, their usual follow-up will be resumed after the release of recovery.

Inclusion in the study lasts 7 days in total, with a follow-up by phone and by a tracking notebook, the last phone call held at 7 days of infusion.

### **Description of study stop, rules or criteria of exclusion for subjects.**

All serious adverse events, defined by: ketamine or its excipients, shock, pushed hypersensitivity reaction hypertensive greater than 180/110 defined as hypertensive emergency according to the HAS, a depression respiratory causing a desaturation < 92% in air, a marked psychodysleptique reaction causing a major stir, that can be linked to the administration of the product will immediately stop the infusion, supported by a doctor specializing in Anaesthesia-resuscitation and the statement from pharmacovigilance and the ANSM.

Each observation will include a reporting of serious adverse events card.

The patient will be analysed in the study for intention to treat analysis, the last pain expressed will be chosen as main analysis on which the study will be judged.

Per-protocol analysis will also take place, excluding patients who have not benefited from the full dose of ketamine.

Any withdrawal of consent before the infusion will result in the exclusion of the subject of the study.

Withdrawal of consent after the end of the infusion, will lead to the choice of the subject, an analysis by intention to treat if the patient accepts the conservation of already saved data or also if it wishes the ouster of the subject of the study so that the deletion of all the data related to the patient, in agreement with the notion of free consent informed, revocable at any time.

The study will end permanently after the 48<sup>th</sup> patient tracking.

Is 7 days after the inclusion and treatment of the 48<sup>th</sup> patient (see calculation of the number of subjects needed here below)

## **Safety assessment and management of serious events**

The investigator has the responsibility to report every adverse events.

### **Definitions**

**Adverse event** : any harmful event occurring in a person who lends itself to biomedical research, that this event is related to research or the product on which this research is defined as adverse event

**Side effect:** all adverse event due to research.

We class them in subclasses:

**-Serious expected adverse effect:** already mentioned in the summary of the characteristics of the product for drugs with permission of placing on the market as is the case in our study. This definition also applies to the test drug when administered to a population off-label of the AMM.

**-Unexpected serious adverse:** if its nature, severity or evolution differ from those described in the most recent version of the brochure for investigators or the summary of the characteristics of the drug.

**Serious adverse event** : any event or adverse reaction which results in death, is endangering the life of the person who lends itself to research, requires hospitalization or prolongation of hospitalization, causes an inability or a significant or long-lasting, handicap or well translates an anomaly or a congenital defect.

The expression "which endangers the life of the person" is reserved for an immediate existential threat, at the time of the adverse event regardless of the consequences of a corrective or palliative therapy.

Deaths, whatever their cause, including when they correspond to a progression of the disease being treated, are considered serious events.

Other events do not meet the above qualifications, may be considered to be "potentially serious", including certain biological abnormalities. The medical judgment of the investigator

or the sponsor may lead to the declaration of such events in the same way that the events "serious."

All new interesting research (or the product used) and may adversely affect the safety of the people who lend themselves to research will be of appropriate urgent safety and information without delay by the promoter from the competent authority and the patients committee protection.

### **Serious adverse event reporting:**

The investigator has the obligation to report within 24 hours to the promoter all serious adverse events occurred in all patients included in the study:

- during the active study,
- in the weeks after the discontinuation of treatment
- within the established time of follow-up of tolerance without treatment, before (phase out wash or withdrawal) or after the active phase.
- After the trial, regardless of the deadline, as no other cause than the research cannot reasonably be offending,

on a form 'Serious adverse event' where will be indicated the date of onset, intensity, the relationship with the treatment (or search), and monitoring. The narrative report should be completed and forwarded to the proponent as soon as new relevant information. Depending on the nature and the severity of the event, copies of anonymised medical records of the patient can be joined, as well as the results of laboratory tests.

When a serious adverse event persists at the end of the study, the investigator will follow the patient until the event is considered to be resolved.

According to the Decree of application No. 2006 - 477 of 26/04/2006 amending the chapter I of title II of book 1 St of the first part of the French code of public health on biomedical research, all suspicions of unexpected serious adverse will be a statement of the proponent ANSM, the CPP and the EMA (via the Eudravigilance basis) for research on a drug, as soon as it is known, and at the latest:

- 7 days after the death or life-threatening event
- 15 days after the onset of the unexpected event for any other SAES.

The proponent will decide on the significance of the serious adverse events that he says and what he doing, particularly with regard to the conduct of research.

The proponent will also adjudicate accountability of the adverse event a test together with the Regional Center of Pharmacovigilance.

The unexpected character will be established by the sponsor from the RCP.

The proponent will keep detailed records of all adverse events which are reported to him by the investigators.

Once a year or on request, the proponent will forward to the ANSM and CPP an annual safety report taking into account all of the available security information.

The proponent will also to the investigators of the study any information that may affect the safety of the people.

### **Oversight Committee**

Given that the active principle assessed as part of this clinical trial is a product that is on the market for several decades and that it is used at the recommended dosages, there we not seem justified to set up an Oversight Committee.

### **Judgment of learning**

The end of the test corresponds to the date of the last visit of the last person in the trial. When a serious adverse event persists at the end of the study, the investigator will follow the patient until the event is considered to be resolved.

A temporary stoppage of the study will be considered when new fact (as defined above) in order to give himself time to reassess the balance of benefits and risks of research jointly with ANSM .

### **Ratings criteria**

#### **Main evaluation criterion**

Decrease (more than 30%) the intensity of neuropathic pain evaluated at the moment on a numeric scale of 10 points between H0 and H4.

#### **Secondary evaluation criteria**

Score of NPSI on H0, J1, J4, J7

Under the NPSI score; H0, J1, J4, J7

Score of depression HADS or Hamilton J0, J7

Pain timeline between J0 and J7.

Painful surface evaluated on mapping H0, J1, J4, J7

Decrease in scores between baseline and H4.

Side effects of the drugs evaluated H0 and H4 of the end of the infusion then in J1.

Auto assessment of relief of pain and mood improvement at 7 days after infusion.

Blood assays pre administration of Ketamine then H4 after end of Directors of: serotonin (5-HT), kynurenine (KYN), indoleamine 2, 3-dioxygenase 1 (IDO1) activity (ratio KYN/TRP), kynurenic acid (KA) and quinolinic acid (QA), as well as 3 proinflammatoires cytokines  $IL-1\beta$ , IL-6, and TNF -  $\alpha$

### **Patient selection, exclusion and data collected.**

#### **The criteria for inclusion:**

- SCI with central neuropathic pain with or without bed sores.
- Adults speaking and understanding the French
- With chronic neuropathic pain, according to the IASP definition
- Painful intensity  $> \text{ or } = 6 / 10$  during the week prior to the inclusion
- Spinal cord injury a few either the origin (traumatic, degenerative, tumor, post operative), responsible for paraplegia in a chronic state.
- Able to give their informed consent after a clear, fair and appropriate information
- Having given their agreement by a written consent signature.

#### **No inclusion criteria:**

- Patients with a hypersensitivity to ketamine or one of its excipients.
- Another Interventional trial participation, or participation in another trial interrupted for less than 3 months.

- Patient unable to give their consent
- Pregnancy or lactation underway
- Refusal of consent signature
- Cardiovascular diseases particularly associated with rhythm disorders and severe heart failure, coronary, discovered by examination, ECG or biological assessment or known.
- HTA unstabilized > 180/100 mmHg
- Severe hepato cellular and / or renal failure.
- For the group without sores, lack of ongoing inflammatory pathology noted by the interrogation (fever, sepsis, urinary tract infection)

**Exclusion criteria:**

As defined above, any adverse product will lead to the immediate cessation of the infusion however the patient will be analysed in the study for an intention to treat analysis. If it refuses the analysis or withdraws consent at any time of the study patients will be excluded from the study in accordance with best practices.

After the duration of 7 days of participation and follow-up, the patient will be released the study as planned in the Protocol (end of final follow-up).

**Data collected on patients:**

These data will include: full name, Date of birth, the patient's Age, height, weight, BMI, sex, usual treatments, Presence of allergy, medical conditions, age of evolution of chronic pain, spinal cord injury, the more important pain in the week prior to the inclusion. Score NPSI, HADS Score, painful Surface evaluated on mapping, Patient having already benefited from infusion of ketamine before, history of use of other non-drug therapies for treatment of chronic pain.

The data collected during the study will be for 7 days with the periods already mentioned: Score of NPSI on H0, J1, J4, J7, NPSI underscore; H0, J1, J4, J7, Score of depression HADS J0, J7 (for all elements in H1 and H4 previous evaluation by the clinician investigator, J1 J4 J7 by a self-report filled at home or by telephone call)

Painful surface evaluated on H0, J1, J4, J7 (H1 and H4 by the clinician investigator, J1 J4 J7 by the patient at home on a sheet displaying the human body).

Regarding the lost to follow-up and missing data, the most pejorative result already gathered about each score will be taken as a reference to complete missing data, for analysis by intention to treat.

Two blood samples will be carried out on each patient. The first will arrive in SSPI before infusion of ketamine. The following sample will be 4 hours after the end of the infusion or 6 hours after the start of the infusion in outpatient service. Sampling and dosing methodology is explained below.

In addition 24 samples will be collected without ketamine infusion (12 patients with bedsores and 12 without), to assess the effect of inflammation on kynurenine pathway.

### **Methodology of dosage**

Blood samples will be collected after 48 h of a diet serotonin (avoid bananas in particular) and tryptophan (chocolate to be avoided) in Vacutainer 7 mL containing EDTA tubes.

After gentle inversions of the tubes (agitation brutal would cause damaging platelet activation with the determination of serotonin, almost exclusively contained in platelets) total 500  $\mu$ L of blood are immediately frozen ( $-20^{\circ}$  C or  $-80^{\circ}$  C). The rest of each sample is centrifuged at  $4^{\circ}$  C and 2500 g for 15 minutes and the resulting plasma is aliquote under 500  $\mu$ L and frozen at  $-80^{\circ}$  C until analysis. Blood serotonin and tryptophan plasma will be measured by HPLC(31). Kynurenic acid and kynurenine will be also measured by HPLC according to Fujigaki, Swartz and al and al respectively(32.33). For his part, quinolinique acid will be measured by LC - MS(34). The kynurenine/tryptophan ratio will be conventionally used as index of activity IDO1.

Cytokines il1beta, IL6 and TNFalpha will be measured by electrochimiluminescence on a multiplex platform (35) .

### **Drugs allowed or stopped during and before the test**

Our population being affected by chronic pain, many treatments to target pain are generally used. The usual treatment of patients will be continued before, during and at the end of the study.

Painkillers of tier 1, 2 or 3. Anti epileptic on pain neuropathic, antidepressants (SSRIS, MAOIS, tricyclics...). None of these drugs will prohibit participation in the study however we will proceed with a compendium of the various treatments by patients.

Ketamine can potentiate the neuromuscular blocking atracurium and the tubocurarine including respiratory depression with apnea. The concomitant administration of ketamine with halogenated anesthetic agents may extend the elimination half-life of ketamine and delay the recovery phase. Our patients are not surgical patients, none will have received this type of product before the infusion.

Co-administration of theophylline may lower the convulsive threshold. No administration of Theophylline is scheduled.

Only bananas and chocolate will be an eviction during the 48 hours preceding blood sampling in order not to distort the dosages of serotonin and tryptophan.

### **Procedures to assess compliance of subjects to treatment**

The infusion being in post operative monitoring room for a period of two hours. Compliance assessment can be done without bias.

In the follow-up phone calls and self-report at home will be considered follow-up. Missing data management has already been clarified above.

### **Assessment of treatment effectiveness**

The effectiveness of the treatment will be judged on a reduction of more than 30% of the intensity of neuropathic pain evaluated at the moment on a numeric scale of 10 points between H0 (before infusion) and H4 (after the end of the infusion). This criterion will be assessed by one of the investigators of the study.

### **Assessment of the safety of the treatment**

Infusion being made in recovery room, the usual follow-up of a patient in recovery room will be arranged: decision-making of the constants every 15 minutes including the oxygen saturation, blood pressure, heart rate, awareness of Glasgow score, the respiratory rate.

Supervision of one hour after the end of the infusion will be implemented.

The release of recovery room will be one hour after the end of the infusion and with the usual criteria of output with Aldrete score.

Any adverse event during infusion will be reported to a doctor Anaesthesiologist resuscitator and will be declared.

If an adverse event occurs a period of hospitalization is equal to 5 times the half-life (3 hours about ketamine), more than 15 hours will be organized until total elimination of the product.

### **Sample size and statistical analysis**

After data from a study underway by our team (study LIKE), the standard deviation of instant pain score is of 1.4 on the same model. We considered that an improvement of 30% in the score of the intensity is relief significant clinic. Based on these figures and assuming a risk  $\alpha = 0.05$  and a risk  $\beta = 0.90$ , and using a one-sided Student's T test for a comparison of the 2 to 2 groups the minimum calculated sample size is 12 patients analyzed per group (for a total of 48 patients).

After checking the normality of distributions, comparison of continuous variables (Score, NPSI, pain, depression and biology Score) between the two groups will be analyzed with the Student's T test, variables with a no normal distribution will be analyzed with the non-parametric Mann-Whitney U test.  $p < 0.05$  was considered statistically significant p-values. R and SPSS software will be used for the production of statistics.

As part of a master of Pharmacology 2 to be made for may 2018, an interim analysis will be carried out by end April 2018, that this will have the same criteria as the final analysis. A security assessment will be also carried out at this time and an assessment of the derivatives to the Protocol.

Both analyses above cited will be intention to treat, all randomized subjects will be included. Management of the lost will be extrapolating value worst case being investigated for missing data. Patients withdrawing consent during the study without desiring the removal of their data will be analyzed. If an application for withdrawal with withdrawal of the data then patients won't be analyzed.

### **Access to the sources and documents related to the research.**

Protection of research participants will be an anonymisation of the data recording in secure files. A declaration to the CNIL has been registered for this search No. 2122369 v 0 as of November 21, 2017.

Access to the source file, anonymised data collection will be left in an audit requested on the study.

### **Quality control and Assurance**

For our study insurance civil liability promoter of Interventional research under article L 1121-1 of the Code of public health is subscribed to hospital society of mutual assurances with the number of contract No. 124.626.

To ensure quality control satisfactory we will put in place standardized operating procedures (POS) with standardized patients support instructions given to investigators of the study. Each patient will have a specification of anonymized observation which will include all identified information, the collection different scores used in the study as well as a record of serious adverse event reporting. These notebooks of observation will be kept throughout the study and one year after the end (last patient included either 7 days after the end of the 48<sup>th</sup> patient inclusion).

### **Direct benefit:**

Patients will be able to benefit from treatment with ketamine and the support and follow-up pain specialist for their refractory neuropathic pain.

If patients included in this study have a real clinical benefit, this treatment may be proposed outside the clinical trial. Then, they will be given priority in the queue.

For society this study will allow progress in the potential effectiveness of ketamine on chronic pain, hypothesis put forward in cancer pain and other chronic pain but for which we still lack of data sufficient to prove its benefit. It will also standardize administration protocols and avoid prolonged high doses of ketamine over several weeks that is responsible of serious adverse (36) .

In addition it will better understand the mechanism of action of the product on this type of pain.

### **Risks incurred and constraints:**

Ketamine at a dose of 1 mg / kg is well tolerated in the clinic and in the various studies around ketamine.

The contraindications of ketamine are allergy, severe hypertension, severe heart failure: patients excluded from our study.

In the conditions of the study, dosage and duration of infusion, the risk of adverse effect is minimal.

### **The constraints for our patients will include:**

Learn about 48 h of infusion a diet serotonin (avoid the bananas in particular) and tryptophan (chocolate to be avoided).

Come to the appointment for the administration of infusion.

Inform the doctor of the research of the use of any medication, as well as of any event occurring during the search.

An accompanying person for the return home for patients on an outpatient basis.

Do not take part in another Interventional trial for the duration of the study.

Being affiliated to a social security scheme or equivalent.

### **Agenda forecast**

- May - June 2017: finalization writing project, application to tender
- September 2017-December 2017: registration of the candidate in MASTER 2, and theoretical courses in parallel, finalisation of the project and administrative procedures (Committee of protection of individuals, filing ANSM, CNIL)
- January 2018 - may 2018: Inclusion of patients and first report on the effectiveness on the first patients included with interim analysis end of April / beginning of may 2018.
- End of year 2018: writing article and dissemination of results at the Congress of pain, anesthesia
- Early 2019: Finalization of article and submission to a journal international

### **Expected end-of-project results:**

Publication of the results in an international journal of high level with oral communication and as a poster in the Congress of anaesthesia, pain and neuroscience. The expected clinical benefits may be a more targeted ketamine use. . This is a preliminary work which would open other opportunities of work, including the controlled randomised studies evaluating different doses and administration of ketamine in this target population.

### **Feasability elements**

Patient recruitment will be made easier because our research takes place within the Department of functional rehabilitation of the Raymond Poincaré hospital in Garches, following one of the largest cohorts of SCI patients in France. A quick calculation on the number of patients hospitalized and monitored for spinal cord injury, allows us to glimpse a potential 90 patients on the 6 month meets our criteria for inclusion. We aim included 48 patients. The feasibility level organizational is real with the participation of the team pain, formed of two anaesthetists accustomed to the administration of ketamine and versed in clinical research.

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